

REMARKS

I. Status Summary

Claims 36, 38-42, 45-59, and 62-65 were pending in the subject U.S. patent application. Claims 64 and 65 were withdrawn by the United States Patent and Trademark Office (hereinafter "the Patent Office") in a Non-Final Official Action dated December 18, 2008 (hereinafter "the Non-Final Official Action") upon the contention that the claims read on unelected subject matter.

Claims 36, 38-42, 45-59, 62, and 63 have been rejected under 35 U.S.C. § 103(a) upon the contention that the claims are unpatentable over PCT International Patent Application Publication No. WO 2004/042024 of Reich et al. (hereinafter "Reich"), in view of U.S. Patent Application Publication No. 2003/0143732 of Fosnaugh et al. (hereinafter "Fosnaugh"), Elbashir et al. (2001) The EMBO Journal 20: 6877-6888 (hereinafter "Elbashir"), Tuschl et al. (2001) The siRNA user guide of the Max Planck Institute for Biophysical Chemistry (hereinafter "Tuschl") and Holen et al. (2003) *Nucleic Acids Research* 31:2401-2407 (hereinafter "Holen").

Claims 36, 38-42, 45-59, 62, and 63 have also been rejected under 35 U.S.C. § 103(a) upon the contention that the claims are unpatentable over Reich, in view of Fosnaugh, Elbashir, Tuschl, and Holen, and further in view of U.S. Patent No. 6,506,559 to Fire et al. (hereinafter "Fire").

The specification has been amended to recite a sequence disclosed in the instant Sequence Listing rather than a sequence available in the GENBANK® database. It is noted that the two sequences were identical as of the priority date of the instant application. Thus, no new matter has been added by the amendments to the specification.

Claim 36 has been amended. Support for the amendments to claim 36 can be found throughout the instant specification as filed, including particularly at page 8, line 6; at page 11, line 6; and at page 20, lines 6-7. Additional support can be found in the Sequence Listing, particularly SEQ ID NO: 7. As such, no new matter has been added by the amendments to claim 36.

Reconsideration of the application as amended and in view of the Remarks presented hereinbelow is respectfully requested.

II. Response to the Withdrawal of New Claims 64 and 65

Claims 64 and 65 have been withdrawn from consideration by the Patent Office upon the contention that they do not constitute a proper genus as each sequence recited is structurally unique.

Applicants respectfully disagree. Particularly, applicants respectfully submit that SEQ ID NOs: 5 and 6 comprise SEQ ID NO: 7 and thus are believed to be within the scope of the constructive election asserted by the Patent Office.

To elaborate, applicants respectfully submit that claim 36 recites *inter alia* a small interfering RNA (siRNA) molecule comprising a sense region and an antisense region, wherein the sense region is between 19 and 30 base pairs in length and comprises the sequence 5'-GATGACATGAAAGCACAGA-3' (SEQ ID NO: 7) and the antisense region comprises a 100% reverse-complement of SEQ ID NO: 7. Stated another way, applicants respectfully submit that claim 36 relates to a genus of siRNA molecules that comprise SEQ ID NO: 7 and an antisense region comprising the 100% reverse-complement of SEQ ID NO: 7. Review of SEQ ID NOs: 5 and 6 demonstrates that these sequences fall within the scope of this genus.

According to the instant specification:

SEQ ID NO: 5 is a generic sequence of an siRNA directed to human HIF-1 α . The sequence comprises 19 nucleotides from a human HIF-1 α cDNA (bases 528-546 of GENBANK[®] Accession No. NM_001530), followed by from 5-9 nucleotides of random sequence, followed by the reverse-complement of bases 528-546 of GENBANK[®] Accession No. NM_001530, followed by from 2-8 nucleotides that form a 3' overhang.

SEQ ID NO: 6 is a specific embodiment of the generic sequence represented by SEQ ID NO: 5.

SEQ ID NO: 7 is the nucleic acid sequence of a sense strand of an siRNA used to target human HIF-1 α .

See Specification at page 13, line 26, through page 14, line 4. The relationship among these sequences is depicted in **Exhibit A**. As shown therein, SEQ ID NO: 7 is a target sequence present within the human HIF-1 α coding sequence. SEQ ID NO: 5 is a generic sequence of an siRNA that comprises SEQ ID NO: 7, and SEQ ID NO: 6 is a specific embodiment of the generic sequence of an siRNA that comprises SEQ ID NO:

7, which is underlined in the hairpin structure of SEQ ID NO: 6 that is depicted at the end of **Exhibit A**.

Therefore, applicants respectfully submit that the Patent Office is believed to be incorrect in its assertion that the sequences of claims 36, 64, and 65 are not considered to constitute a proper genus. Particularly, applicants respectfully traverse the Patent Office's assertion that the sequences do not contain a common structural core, as **Exhibit A** shows that the common structure core is SEQ ID NO: 7. Additionally, applicants respectfully traverse the Patent Office's assertion that the sequence represents a separate region of a target, since each sequence targets SEQ ID NO: 7.

And finally, applicants respectfully traverse the Patent Office's assertion that a search of more than one of the sequences would present an undue burden on the Patent Office. Applicants respectfully submit that a complete search of SEQ ID NO: 7 would be expected to identify all siRNAs that comprise SEQ ID NO: 7, and thus would be expected to identify both SEQ ID NOs: 5 and 6.

Summarily, applicants respectfully submit that the Patent Office is believed to be incorrect in its assertion that the sequences of claims 36, 64, and 65 do not constitute a proper genus, as it is clear that the siRNAs recited in claims 64 and 65 are embodiments of the siRNAs claimed in claim 36.

Accordingly, applicants respectfully request that claims 64 and 65 be rejoined to the instantly pending claims and examined on the merits.

III. Responses to the Rejections under 35 U.S.C. § 103(a)

Claims 36, 38-42, 45-59, 62, and 63 stand newly rejected under 35 U.S.C. § 103(a) upon the contention that the claims are unpatentable over Reich, in view of Fosnaugh, Elbashir, Tuschl, and Holen. Claims 36, 38-42, 45-59, 62, and 63 also stand newly rejected under 35 U.S.C. § 103(a) upon the contention that the claims are unpatentable over Reich, in view of Fosnaugh, Elbashir, Tuschl, and Holen, further in view of Fire.

After careful consideration of the rejections and the Patent Office's bases therefor, applicants respectfully traverse the rejections and submit the following remarks.

III.A. Response to the First Obviousness Rejection

Claims 36, 38-42, 45-59, 62, and 63 have been rejected over Reich, in view of Fosnaugh, Elbashir, Tuschl, and Holen. According to the Patent Office, Reich teaches *inter alia* siRNA molecules that target HIF-1 α mRNA and inhibit the expression of the HIF-1 α gene via RNA interference. The Patent Office alleges that Reich also teaches that the siRNA can comprise two separate strands or can comprise a single molecule in which two complementary portions are base-paired and covalently linked. The Patent Office also alleges that Reich teaches modifications of the siRNA to increase stability and resistance to nuclease digestion.

The Patent Office concedes, however, that Reich does not teach siRNA molecules wherein the sense region comprises instant SEQ ID NO: 7 and the antisense region comprises the reverse complement of SEQ ID NO: 7. The Patent Office asserts, however, that it would have been *prima facie* obvious to perform routine optimization to walk the known HIF-1 α target sequence to design any given siRNA against the sequence in view of the guidelines taught by Elbashir and Tuschl. According to the Patent Office,

With regards specifically to the sense region comprising SEQ ID NO: 7 and the antisense region comprising a reverse complement of instant SEQ ID NO: 7, siRNAs of this genus are within the genus that would result from routine optimization of the guidelines/testing set forth by Elbashir et al., Tuschl et al., and Holen et al. Applicant has not demonstrated any unexpected result for a siRNA comprising the instant sequences, wherein sequences within this genus would have resulted from the rational design of siRNAs to HIF-1 α following the published guidance of Elbashir et al., Tuschl et al., and Holen et al.

Non-Final Official Action at page 10-11.

Without acquiescing to the Patent Office's assertions in support of the obviousness of the instant claims, applicants respectfully submit herewith a DECLARATION OF CHUAN LI, PH.D. PURSUANT TO 37 C.F.R. §1.132 (hereinafter "the Li Declaration"). As set forth therein, the Li Declaration provides evidence that an siRNA comprising SEQ ID NO: 7 has unexpectedly superior activity in downregulating HIF-1 α . In particular, the data presented therein demonstrate that as compared to other

siRNAs that attempt to target HIF-1 α , the siRNA comprising SEQ ID NO: 7 is markedly more effective in downregulating HIF-1 α .

Thus, applicants respectfully submit that even assuming *arguendo* that the Patent Office has established a *prima facie* case of obviousness of the subject matter of claim 36, applicants respectfully submit that the *prima facie* case is believed to be rebutted by this evidence of this unexpectedly superior property which characterizes SEQ ID NO: 7.

Accordingly, applicants respectfully submit that claims 36, 38-42, 45-59, 62, and 63 have been distinguished over Reich in view of Fosnaugh, Elbashir, Tuschl, and Holen. As a result, applicants submit that the specific siRNA molecules of claims 36, 38-42, 45-59, 62, and 63 are not obvious over the cited combination of references, and respectfully request that the instant rejection be withdrawn.

III.B. Response to the Second Obviousness Rejection

Claims 36, 38-42, 45-59, 62, and 63 also have been rejected under 35 U.S.C. § 103(a) upon the contention that the claims are unpatentable over Reich in view of Fosnaugh, Elbashir, Tuschl, and Holen, and further in view of Fire. In addition to the assertions presented in support of the previous rejection, the Patent Office asserts that Fire teaches, *inter alia*, a method of inhibiting the expression of a target gene in a cell comprising introduction of a double-stranded RNA molecule in an amount sufficient to inhibit the expression of the target gene.

Applicants respectfully disagree that Fire supports a rejection of the pending claims under 35 U.S.C. § 103(a). Initially, applicants respectfully note that the instant claims are directed to siRNAs, while the dsRNAs of Fire range from 299 to 1033 base pairs in length, with 15 of the 19 dsRNAs demonstrated being larger than 500 base pairs in length. See Table 1, columns 22-24 of Fire. Applicants respectfully submit that one of ordinary skill in the art would understand after review of the instant specification that Fire does not disclose siRNAs.

Nevertheless, in the interest of facilitating prosecution and without acquiescing to the contentions of the Patent Office, claim 36 has been amended to recite that the sense region of the siRNA is between 19 and 30 base pairs in length. Support for this amendment is found in the instant specification on page 8, line 6; page 11, line 6; and

page 20, lines 6-7, among other places. Thus, no new matter has been added by the instant amendment to claim 36. Applicants respectfully submit that consistent with the Patent Office's indication on page 13 of the Non-Final Official Action, this element that recites a length for the siRNA and is believed to obviate the instant rejection.

Accordingly, applicants respectfully submit that claim 36 has been distinguished from Reich in view of Fosnaugh, Elbashir, Tuschl, and Holen, and further in view of Fire. Claims 38-42, 45-59, 62, and 63 all depend from claim 36, and thus are also believed to be distinguished over the cited combination of references. As a result, applicants respectfully request that the instant rejection of claims 36, 38-42, 45-59, 62, and 63 under 35 U.S.C. § 103(a) be withdrawn at this time. Applicants further respectfully solicit a Notice of Allowance to that effect.

CONCLUSIONS

As a result of the amendments and remarks presented hereinabove, applicants respectfully submit that claims 36, 38-42, 45-59, and 62-65 are in condition for allowance, and respectfully solicit a Notice of Allowance to that effect.

Should there be any minor issues outstanding in this matter, the Examiner is respectfully requested to telephone the undersigned attorney. Early passage of the subject application to issue is earnestly solicited.

Deposit Account

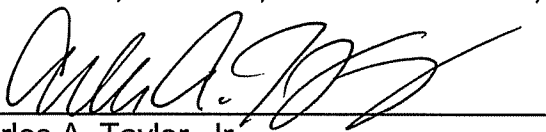
The Commissioner is hereby authorized to charge any underpayment or credit any overpayment of fees associated with the filing of this correspondence to Deposit Account Number 50-0426.

Respectfully submitted,

JENKINS, WILSON, TAYLOR & HUNT, P.A.

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By:



Arles A. Taylor, Jr.

Registration No. 39,395

Customer No. 25297

(919) 493-8000

180/179 PCT/US AAT/PPP/cam